

REMARKS

Opioid drugs, such as morphine, are among the most powerful and widely used analgesics known. These drugs, however, are not without untoward side effects, most notably of which are the sedative and addictive effects of these drugs on the central nervous system (CNS). The present invention provides new opioid drugs that, while retaining activity in the peripheral nervous system, do not substantially affect the CNS, due to the fact that these drugs are less accessible to the CNS. Central to this advantage of these new drugs is the linkage of a charged group, via a spacer, to the nitrogen atom of the basic opioid structure. The charged group, which, by increasing the hydrophilicity of the drug, reduces passage of the drug across the blood-brain barrier into the CNS, has no adverse effects on drug efficiency.

Summary of the Office Action

Claims 1-3, 5, 7-12, 14, 16, 19-25, 28, 29, 31, 33, and 34 are pending in this application. The Examiner has maintained the rejection of claims 1, 23-25, and 33 for lack of enablement. Claims 1-3, 5, 7-12, 14, 19-25, 28, 29, 31, 33, and 34 stand rejected under 35 U.S.C. §112, first paragraph, as containing new matter. Claims 1-3, 5, 7-12, 14, 19-25, 28, 29, 31, 33, and 34 stand rejected under 35 U.S.C. §112, second paragraph, as indefinite. The Examiner has found that claim 16 is allowable if rewritten in independent form. Applicants address these rejections with the following amendments and remarks.

Rejection under 35 U.S.C. §112, paragraph 1, for lack of enablement

Claims 1, 23-25, and 33 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. As a basis for the enablement rejection, the Office Action at paragraph 7 recites "Applicant has amended the spacer to be '1-6

atoms' without defining what these atoms are." Applicants address these rejections by amendment of the claims and with the following remarks.

Applicants have addressed the enablement rejections by amendment of the claims in accordance with language agreed upon in the telephonic interview of February 18, 2004. Specifically, claim 1 has been amended from "(spacer) is a group linking YN to an amidine or guanidine group, wherein YN and said amidine or guanidine group are separated by 1 to 6 atoms" to "(spacer) is a group linking YN to an amidine or guanidine group, wherein YN and said amidine or guanidine group are separated by 1 to 6 carbon atoms." This amendment was proposed by the Examiner to address the enablement rejection of claim 1, and claims dependent thereto.

Furthermore, a potential enablement rejection arises from amendment of the claims 1, 7, and 8 from "R¹ and R³ together form an alkylene or alkenylene of from 2 to 4 carbon atoms to complete a ring including two nitrogen atoms" to "R¹ and R³ together complete a heterocyclic ring including two nitrogen atoms." During the telephonic interview of February 18, 2004, the Examiner agreed that this amendment would not give rise to an enablement rejection in view of the specification and the previously submitted Schlama reference, *J. Org. Chem.*, 62:4200 (1997), which describes a method of preparing the claimed heterocyclic rings.

In view of the amendments made to the claims, Applicants request withdrawal of the enablement rejections.

Rejection under 35 U.S.C. §112, paragraph 1, for new matter

Claims 1-3, 5, 7-12, 14, 19-25, 28, 29, 31, 33, and 34 were rejected under §112, first paragraph for claiming new matter. As a basis for the new matter rejection, the Office Action at paragraph 9 recites:

- a. Q of YNQ in claim 1 is not defined in the claim and it is not described in the specification. Applicant has recited page 4, lines 14 to 26 for support of the amendment. However, only YN-R or Y¹NRR⁴ with specific definitions for R and R⁴ are disclosed.
- b. 'R¹ and R³ together form an alkylene or alkenylene of from 2 to 4 carbon atoms to complete a ring including two nitrogen atoms' found in claims 7, 8 has no description in the specification, even though the imidazolyl of claim 9 falls within this genus.
- c. YN(CH₂)_n-NH₂ of claims 19, 34, YN(CH₂)_n-(NH)0-1-CN of claims 20-22, the compound of formula V of claim 34, and the reactions thereof, are not described in the specification.

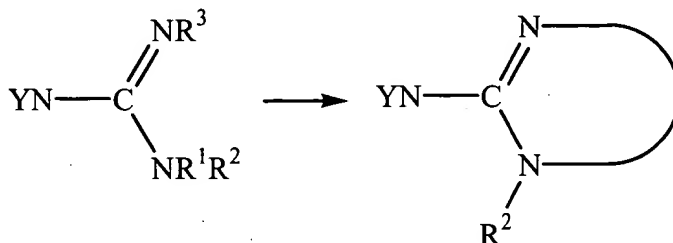
The rejection is applicable to claims dependent on the above claims.

Applicants have addressed these rejections by amendment of the claims and with the following arguments.

Applicants have addressed the rejection of claim 1, and claims dependent thereto, by amendment of the claims in accordance with language agreed upon in the telephonic interview of February 18, 2004. Specifically, claim 1, and claims dependent thereto, have been amended from "YN-Q" to "YN-R" and from "Q" to "R" so that the symbols used in the claims mirror those in the specification at page 4, lines 14-21.

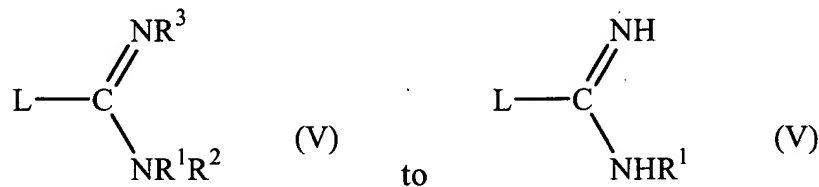
Applicants have addressed the rejection of claims 1, 7, and 8 by amendment of the claims in accordance with language agreed upon in the telephonic interview of February 18, 2004. Specifically, claims 1, 7, and 8 have been amended from "R¹ and R³ together form an alkylene or alkenylene of from 2 to 4 carbon atoms to complete a ring including two nitrogen atoms" to "R¹ and R³ together complete a heterocyclic ring including two nitrogen atoms."

Support for these amendments of claims 1, 7, and 8 is found in the specification at page 4, line 30, to page 5, line 20. As shown below, when R¹ and R³ together complete a ring, the ring is necessarily a heterocyclic ring including two nitrogen atoms.



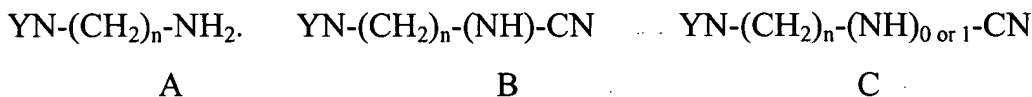
Two examples of heterocyclic rings including two nitrogen atoms, imidazolyl and imidazolinyl rings, are provided at page 5, line 15, of the specification.

Applicants have addressed the rejection of claim 34 by amendment of formula (V) from:



Support for the amendment of claim 34 is found in the specification at page 38, line 35. Reactions involving the compound of formula (V) are provided at page 39, line 5.

The Examiner has rejected claims 19 and 34 for reciting the formula A, below, rejected claims 20 and 21 for reciting the formula B, below, and rejected claim 22 for reciting formula C, below.



Applicants traverse the rejection of claims 19-22 and 34 with the following remarks.

*The Subject Matter of the
Claim Need not be Described Literally*

To satisfy the written description requirement, the application as filed “must . . . convey with reasonable clarity to those skilled in the art that . . . [the inventor] was in possession of the invention.” *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). The original disclosure need not provide *in haec verba* support for the claimed subject matter at issue. *See In re Wright*, 866 F.2d 422, 425, 9 USPQ2d 1649, 1651 (Fed. Cir. 1989). Rather, one skilled in the art, reading the original disclosure, must

“immediately discern the limitation at issue” in the claims. *Waldemar Link GmbH & Co. v. Osteonics Corp.*, 32 F.3d 556, 558, 31 USPQ2d 1855, 1857 (Fed. Cir. 1994). As the Federal Circuit recently explained:

The written description requirement does not require the applicant “to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (citations omitted). Thus, § 112, ¶ 1 ensures that, as of the filing date, the inventor conveyed with reasonable clarity to those of skill in the art that he was in possession of the subject matter of the claims.

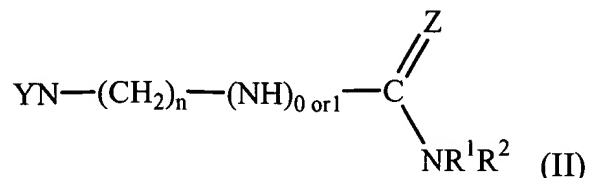
Union Oil Co. of Calif. v. Atlantic Richfield Co., 208 F.3d 989, 997, 54 USPQ2d 1227, 1232 (Fed. Cir. 2000).

*Applicants are not Required
to Recite the Claimed Formula
within the Specification*

Applicants note that support in the disclosure is not required to be in the form of an exact recitation of the formulas in question. With respect to the claimed formulas, the analysis must take into account which syntheses one skilled in the art would consider inherently supported by the original disclosure. *In re Wertheim*, 541 F.2d 258, 191 USPQ 90 (CCPA 1976) is controlling on this point. In *Wertheim*, the CCPA held that the specification supported the claimed range, even though the precise range of the claim was not repeated verbatim in the specification. *Id.* at 263. *See also Union Oil*, 208 F.3d at 1000, 54 USPQ2d at 1235 (applying *Wertheim* and holding that “the disclosure at the time of filing taught one of skill in the art that the inventors possessed the subject matter of the later [added] claims”).

*There is Support for
the Formulas of Claims 19-22 and 34*

The specification, beginning at page 11, line 19, describes a variety of synthetic approaches for making the compounds of formula (II), shown below.

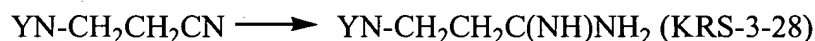


One skilled in the art would recognize that the synthetic schemes provided on pages 11 to 14 for compounds in which n of formula II is 0 would be equally useful for the preparation of compounds in which a methylene linker separates the opioid (YN) from the amidinium or guanidinium group. Furthermore, synthetic schemes involving compounds of formula II which include a methylene linker are reduced to practice in the examples as follows.

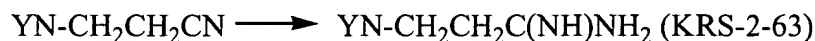
Example 13, page 20:



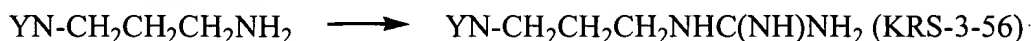
Example 16, page 21:



Example 20, page 25-26:



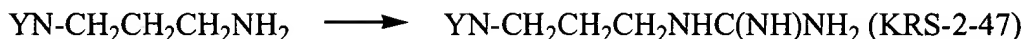
Example 19, pages 23-24:



Example 21, pages 27-28:



Example 22, pages 29-30:



There are a variety of ways in which an applicant can demonstrate possession of the invention, including words, formulas, or by a reduction to practice. See MPEP 2163.

In view of the amendments and arguments presented above, Applicants request withdrawal of the new matter rejections.

Rejection under 35 U.S.C. §112, paragraph 2, for indefiniteness.

Claims 1-3, 5, 7-12, 14, 19-25, 28, 29, 31, 33, and 34 were rejected under §112, second paragraph, as indefinite. As a basis for the indefiniteness rejection, the Office Action at paragraph 10 recites:

- a. Claim 1, second to last line, the term ‘comprising’ in ‘opiod of formula YN-Q comprising’ is open-ended and is therefore indefinite.
 - b. Claim 19, it is unclear how the recited process would make compounds of claim 7 other than those wherein Z is NR3 and wherein R2 and R3 are both H.
 - c. Claims 20, 21, 22 it is unclear how the recited process would make compounds of claim 7 other than those wherein Z is NR3 and wherein R2 is alkyl or H and R3 is H.
- The rejection is applicable to claims dependent on the above claims.

Applicants have addressed these rejections by amendment of the claims and with the following arguments.

Applicants have addressed the rejection of claim 1 by amendment of the claims in accordance with language agreed upon in the telephonic interview of February 18, 2004. Specifically, claim 1 has been amended from “comparison to any opiod of formula YN-Q comprising an organic residue YN...” to “comparison to any opiod of formula YN-R wherein YN of YN-R is identical to

YN of said compound and R of YN-R is H, $-\text{CH}_2\text{CH}=\text{CMe}_2$, phenethyl, cyclopropyl, or an alkyl of 1 to 6 carbon atoms.” This amendment was proposed by the Examiner to address the indefiniteness rejection of claim 1.

Support for the amendment of claim 1 is found in the specification at page 4, lines 16-21, and in the tables of compounds at pages 9 and 10, which recite a variety of specific opioids containing various R groups, including $-\text{CH}_2\text{CH}=\text{CMe}_2$ and phenethyl.

Applicants have addressed the rejection of claims 19-22 by removing the reference to claim 7 and inserting the narrower formula for the types of products produced by each reaction.

Support for the amendment of claims 19-22 is found in the reactions schemes provided on pages 11 to 14 and in formula II at page 4, line 7, to page 5, line 20.

In view of these amendments, Applicants request withdrawal of the indefiniteness rejections.

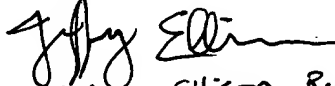
Conclusion

Applicants submit that the claims are now in condition for allowance and such action is respectfully requested. To expedite prosecution Applicants request a telephonic interview with the Examiner to discuss any remaining rejections and objections. The Examiner is invited to call the undersigned at 617-428-0200.

Applicants note that the Form PTO-1449 that was submitted with an Information Disclosure Statement filed on September 30, 2003 has not been initialled and returned, and hereby requests that it be initialled and returned with the next communication.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,


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Date: February 19, 2004

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50124.005001 reply to OA mailed 12.19.03